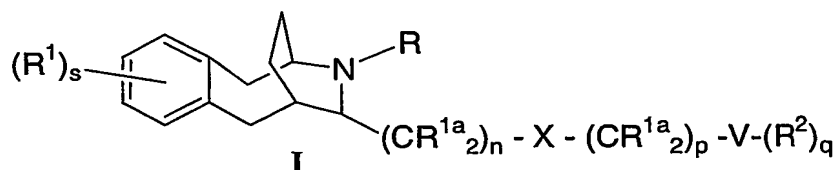


## WHAT IS CLAIMED IS:

1. A compound of Formula I



5 wherein

R is selected from

- 1) H,
- 2) OR<sup>4</sup>,
- 3) unsubstituted or substituted C<sub>1</sub>-C<sub>10</sub> alkyl,
- 10 4) unsubstituted or substituted aryl,
- 5) unsubstituted or substituted C<sub>3</sub>-C<sub>10</sub> cycloalkyl,
- 6) unsubstituted or substituted heterocycle,
- 7) -C(O)R<sup>4</sup>,
- 8) C(O)OR<sup>4</sup>, and
- 15 9) C(O)N(R<sup>4</sup>)<sub>2</sub>;

R<sup>1a</sup> is independently selected from

- 1) H,
- 2) unsubstituted or substituted C<sub>1</sub>-C<sub>6</sub> alkyl, and
- 20 3) OR<sup>4</sup>;

R<sup>1b</sup> is independently selected from

- 1) H, and
- 2) unsubstituted or substituted C<sub>1</sub>-C<sub>6</sub> alkyl;

25

X is selected from

- 1) a bond,

- 2) C(O),
- 3) O, and
- 4) NR<sup>4</sup>;

5 R<sup>1</sup> is independently selected from

- 1) H,
- 2) halo,
- 3) OR<sup>4</sup>,
- 4) NO<sub>2</sub>,
- 10 5) -S(O)<sub>m</sub>R<sup>4</sup>,
- 6) CN
- 7) unsubstituted or substituted C<sub>1</sub>-C<sub>10</sub> alkyl,
- 8) unsubstituted or substituted aryl,
- 9) unsubstituted or substituted C<sub>2</sub>-C<sub>6</sub> alkenyl,
- 15 10) unsubstituted or substituted C<sub>3</sub>-C<sub>10</sub> cycloalkyl,
- 11) unsubstituted or substituted alkynyl,
- 12) unsubstituted or substituted heterocycle,
- 13) -C(O)R<sup>4</sup>,
- 14) C(O)OR<sup>4</sup>,
- 20 15) C(O)N(R<sup>4</sup>)<sub>2</sub>,
- 16) S(O)<sub>m</sub>N(R<sup>4</sup>)<sub>2</sub>, and
- 17) N(R<sup>4</sup>)<sub>2</sub>;

V is selected from

- 25 1) H,
- 2) CF<sub>3</sub>,
- 3) aryl,
- 4) heterocycle, and

5) C<sub>3</sub>-C<sub>10</sub> cycloalkyl;

R<sup>2</sup> is independently selected from

- 1) H,
- 5 2) unsubstituted or substituted C<sub>1</sub>-C<sub>10</sub> alkyl,
- 3) -(CR<sup>1b</sup>)<sub>t</sub>OR<sup>4</sup>,
- 4) Halo,
- 5) CN,
- 6) NO<sub>2</sub>,
- 10 7) CF<sub>3</sub>,
- 8) -(CR<sup>1b</sup>)<sub>t</sub>N(R<sup>4</sup>)<sub>2</sub>,
- 9) -C(O)OR<sup>4</sup>,
- 10) -C(O)R<sup>4</sup>,
- 11) -S(O)<sub>2</sub>R<sup>4</sup>,
- 15 12) -(CR<sup>1b</sup>)<sub>t</sub>NR<sup>4</sup>(CR<sup>1b</sup>)<sub>t</sub>R<sup>5</sup>,
- 13) -(CR<sup>1b</sup>)<sub>t</sub>S(O)<sub>m</sub>NR<sup>4</sup>,
- 14) -C(O)OR<sup>4</sup>R<sup>5</sup>,
- 15) -NR<sup>4</sup>C(O)R<sup>4</sup>,
- 16) unsubstituted or substituted aryl, and
- 20 17) unsubstituted or substituted heterocycle;

R<sup>4</sup> is independently selected from

- 1) H,
- 2) unsubstituted or substituted C<sub>1</sub>-C<sub>10</sub> alkyl,
- 25 3) unsubstituted or substituted C<sub>3</sub>-C<sub>10</sub> cycloalkyl,
- 4) unsubstituted or substituted aryl,
- 5) unsubstituted or substituted heterocycle, and
- 6) CF<sub>3</sub>;

R<sup>5</sup> is independently selected from

- 1) unsubstituted or substituted aryl, and
- 2) unsubstituted or substituted heterocycle;

5 m is independently 0, 1 or 2;

n is 0 to 6;

p is 0 to 6;

q is 0 to 6, provided that when V is H or CF<sub>3</sub>, q is 0; and

s is 0 to 16;

10 t is independently 0 to 6;

or a pharmaceutically acceptable salt or stereoisomer thereof.

2. The compound according to Claim 1 wherein R<sup>1b</sup>, R<sup>4</sup>, R<sup>5</sup> and  
15 variables m, n, p, q and t are as defined in Claim 1 and

R is selected from

- 1) H,
- 2) OR<sup>4</sup>,
- 20 3) unsubstituted or substituted C<sub>1</sub>-C<sub>10</sub> alkyl, and
- 4) unsubstituted or substituted aryl.

R<sup>1a</sup> is independently selected from

- 1) H, and
- 25 2) unsubstituted or substituted C<sub>1</sub>-C<sub>6</sub> alkyl;

X is selected from

- 1) a bond, and
- 2) C(O);

30

$R^1$  is independently selected from

- 1) H,
- 2) halo,
- 3)  $OR^4$ ,
- 5 4)  $N(R^4)_2$ ,
- 5)  $NO_2$ , and
- 6) unsubstituted or substituted  $C_1$ - $C_{10}$  alkyl;

V is selected from

- 10 1) H,
- 2)  $CF_3$ ,
- 3) aryl, and
- 4) heterocycle;

15  $R^2$  is independently selected from

- 1) H,
- 2) unsubstituted or substituted  $C_1$ - $C_{10}$  alkyl,
- 3)  $-(CR^{1b})_tOR^4$ ,
- 4) Halo,
- 20 5) CN,
- 6)  $NO_2$ ,
- 7)  $CF_3$ ,
- 8)  $-(CR^{1b})_tN(R^4)_2$ ,
- 9)  $-C(O)OR^4$ ,
- 25 10)  $-(CR^{1b})_tS(O)_mNR^4$ ,
- 11)  $-(CR^{1b})_tNR^4(CR^{1b})_tR^5$ ,
- 12)  $-C(O)OR^4R^5$ , and
- 13)  $-NR^4C(O)R^4$ ;

s is 0 to 6;

or a pharmaceutically acceptable salt or stereoisomer thereof.

3. The compound according to Claim 1 wherein R<sup>1b</sup>, X, R<sup>1</sup>, R<sup>2</sup>,  
5 R<sup>4</sup>, R<sup>5</sup> and variables m and t are as defined above and:

R<sup>1a</sup> is independently selected from

- 1) H, and
- 2) unsubstituted or substituted C<sub>1</sub>-C<sub>6</sub> alkyl;

10

V is selected from

- 1) aryl, and
- 2) heterocycle;

15 n is 0 to 3;

p is 0 to 3;

q is 0 to 3;

or a pharmaceutically acceptable salt or stereoisomer thereof.

20

4. A compound that is:

(6*R*,9*S*,11*R*)-11-phenyl-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo  
[a][8]annulene;

25 (6*R*,9*R*,11*S*)-11-phenyl-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo  
[a][8]annulene;

(6*S*,9*R*,11*R*)-11-phenyl-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo  
[a][8]annulene;

30

(6*S*,9*R*,11*S*)-11-phenyl-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo  
[a][8]annulene;

- (6*S*,9*R*,11*S*)-11-benzyl-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo  
[*a*][8]annulene;
- 5 (6*S*,9*R*,11*R*)-11-benzyl-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo  
[*a*][8]annulene;
- (6*R*,9*S*,11*S*)-11-benzyl-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo  
[*a*][8]annulene;
- 10 (6*R*,9*S*,11*R*)-11-benzyl-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo  
[*a*][8]annulene;
- (6*S*,9*R*,11*S*)-11-(3-bromobenzyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)  
benzo[*a*][8]annulene;
- 15 (6*S*,9*R*,11*R*)-11-(3-bromobenzyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)  
benzo[*a*][8]annulene;
- (6*R*,9*S*,11*S*)-11-(3-bromobenzyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)  
20 benzo[*a*][8]annulene;
- (6*R*,9*S*,11*R*)-11-(3-bromobenzyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)  
benzo[*a*][8]annulene;
- 25 (6*S*,9*R*,11*S*)-11-(1,3-benzodioxol-5-ylmethyl)-5,6,7,8,9,10-hexahydro-6,9-  
(epiminomethano)benzo[*a*][8]annulene;
- (6*S*,9*R*,11*R*)-11-(1,3-benzodioxol-5-ylmethyl)-5,6,7,8,9,10-hexahydro-6,9-  
(epiminomethano)benzo[*a*][8]annulene;
- 30 (6*R*,9*S*,11*S*)-11-(1,3-benzodioxol-5-ylmethyl)-5,6,7,8,9,10-hexahydro-6,9-  
(epiminomethano)benzo[*a*][8]annulene;
- (6*R*,9*S*,11*R*)-11-(1,3-benzodioxol-5-ylmethyl)-5,6,7,8,9,10-hexahydro-6,9-  
35 (epiminomethano)benzo[*a*][8]annulene;

- (6*S*,9*R*,11*S*)-11-(3-bromobenzyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulen-4-amine;
- 5 (6*S*,9*R*,11*R*)-11-(3-bromobenzyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulen-4-amine;
- (6*R*,9*S*,11*S*)-11-(3-bromobenzyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulen-4-amine;
- 10 (6*R*,9*S*,11*R*)-11-(3-bromobenzyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulen-4-amine;
- (6*S*,9*R*,11*S*)-11-(3-bromobenzyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulen-1-amine;
- 15 (6*S*,9*R*,11*R*)-11-(3-bromobenzyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulen-1-amine;
- (6*R*,9*S*,11*S*)-11-(3-bromobenzyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulen-1-amine;
- 20 (6*R*,9*S*,11*R*)-11-(3-bromobenzyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulen-1-amine;
- (6*S*,9*R*,11*S*)-11-(1-benzofuran-2-ylmethyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulene;
- 25 (6*S*,9*R*,11*R*)-11-(1-benzofuran-2-ylmethyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulene;
- 30 (6*R*,9*S*,11*S*)-11-(1-benzofuran-2-ylmethyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulene;
- (6*R*,9*S*,11*R*)-11-(1-benzofuran-2-ylmethyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulene;
- 35



- (6*S*,9*R*,11*S*)-11-(1,3-oxazol-2-ylmethyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulene;
- 5 (6*S*,9*R*,11*R*)-11-(1,3-oxazol-2-ylmethyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulene;
- (6*R*,9*S*,11*S*)-11-(1,3-oxazol-2-ylmethyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulene;
- 10 (6*R*,9*S*,11*R*)-11-(1,3-oxazol-2-ylmethyl)-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulene;
- (6*S*,9*R*,11*S*)-11-isopentyl-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulene;
- 15 (6*S*,9*R*,11*R*)-11-isopentyl-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulene;
- (6*R*,9*S*,11*S*)-11-isopentyl-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulene;
- 20 (6*R*,9*S*,11*R*)-11-isopentyl-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulene;
- 25 or a pharmaceutically acceptable salt or stereoisomer thereof.

5. A compound according to Claim 4 that is:

- (6*R*,9*S*,11*R*)-11-phenyl-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulene;
- 30 (6*R*,9*R*,11*S*)-11-phenyl-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulene;
- (6*S*,9*R*,11*R*)-11-phenyl-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo[*a*][8]annulene;
- 35

(6*S*,9*R*,11*S*)-11-phenyl-5,6,7,8,9,10-hexahydro-6,9-(epiminomethano)benzo  
[a][8]annulene;

or a pharmaceutically acceptable salt or stereoisomer thereof.

5

6. A pharmaceutical composition which is comprised of a  
compound in accordance with Claim 1 and a pharmaceutically acceptable carrier.

7. A method of modulating the catalytic activity of protein kinases  
10 in a mammal in need thereof comprising contacting the protein kinase with a  
compound of Claim 1.

8. The method of Claim 7 wherein the protein kinase is an RTK.

9. The method of Claim 8, wherein the RTK is selected from IR,  
15 IGF-1R and IRR.

10. A method of treating or preventing a PK-related disorder in a  
mammal in need thereof comprising administering to said mammal a therapeutically  
20 effective amount of a compound of Claim 1.

11. A method of Claim 10, wherein the PK-related disorder is an  
IGF-1R-related disorder selected from:

- 25
- 1) cancer,
  - 2) diabetes,
  - 3) an autoimmune disorder,
  - 4) a hyperproliferation disorder,
  - 5) aging,
  - 6) acromegaly, and
  - 30 7) Crohn's disease.

12. A method of treating cancer in a mammal in need of such treatment comprising administering to said mammal a therapeutically effective amount of a compound of Claim 1.

5 13. A method of treating retinal vascularization comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of Claim 1.

10 14. A method of treating cancer which comprises administering a therapeutically effective amount of a compound of Claim 1 in combination with a second compound selected from:

- 1) an estrogen receptor modulator,
- 2) an androgen receptor modulator,
- 3) retinoid receptor modulator,
- 15 4) a cytotoxic agent,
- 5) an antiproliferative agent,
- 6) a prenyl-protein transferase inhibitor,
- 7) an HMG-CoA reductase inhibitor,
- 8) an HIV protease inhibitor,
- 20 9) a reverse transcriptase inhibitor, and
- 10) an angiogenesis inhibitor.

15 15. The method of Claim 14, wherein the second compound is an estrogen receptor modulator selected from tamoxifen and raloxifene.

25 16. A method of treating cancer which comprises administering a therapeutically effective amount of a compound of Claim 1 in combination with radiation therapy.

17. The method of Claim 16 wherein radiation therapy is also administered.
18. A method of treating cancer which comprises administering a therapeutically effective amount of a compound of Claim 1 and paclitaxel or trastuzumab.
19. A method of treating or preventing cancer which comprises administering a therapeutically effective amount of a compound of Claim 1 and a GPIIb/IIIa antagonist.
20. The method of Claim 19 wherein the GPIIb/IIIa antagonist is tirofiban.
21. A method of treating or preventing cancer which comprises administering a therapeutically effective amount of a compound of Claim 1 in combination with a COX-2 inhibitor.